Abstract #41 | Poster

T-Cell Exhaustion and Myeloid Rewiring During Murine CLL Progression Uncovered by High-Dimensional Spectral Cytometry

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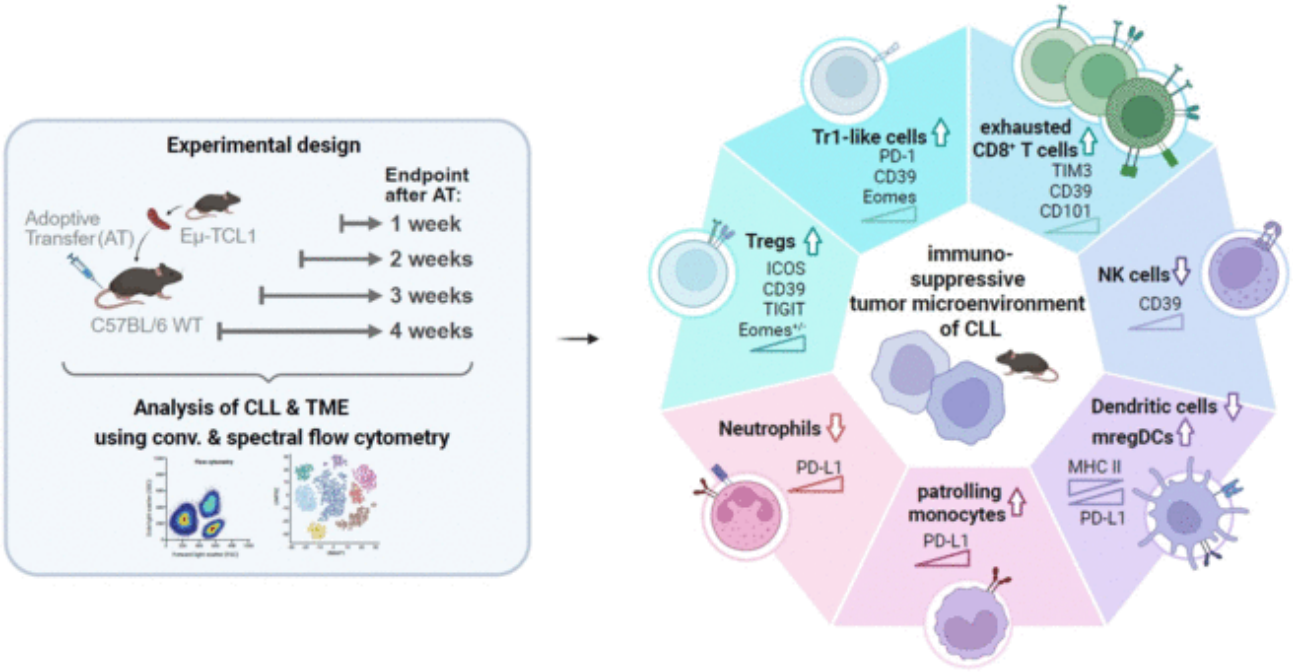
Chronic lymphocytic leukemia (CLL) displays pronounced clinical heterogeneity that cannot be fully explained by genetic alterations alone, highlighting the essential influence of the tumor microenvironment on disease progression and therapeutic resistance. To capture the temporal development of immune dysregulation in CLL, we employed the Eμ-TCL1 adoptive transfer model coupled with longitudinal high-dimensional spectral flow cytometry to comprehensively profile both lymphoid and myeloid compartments.

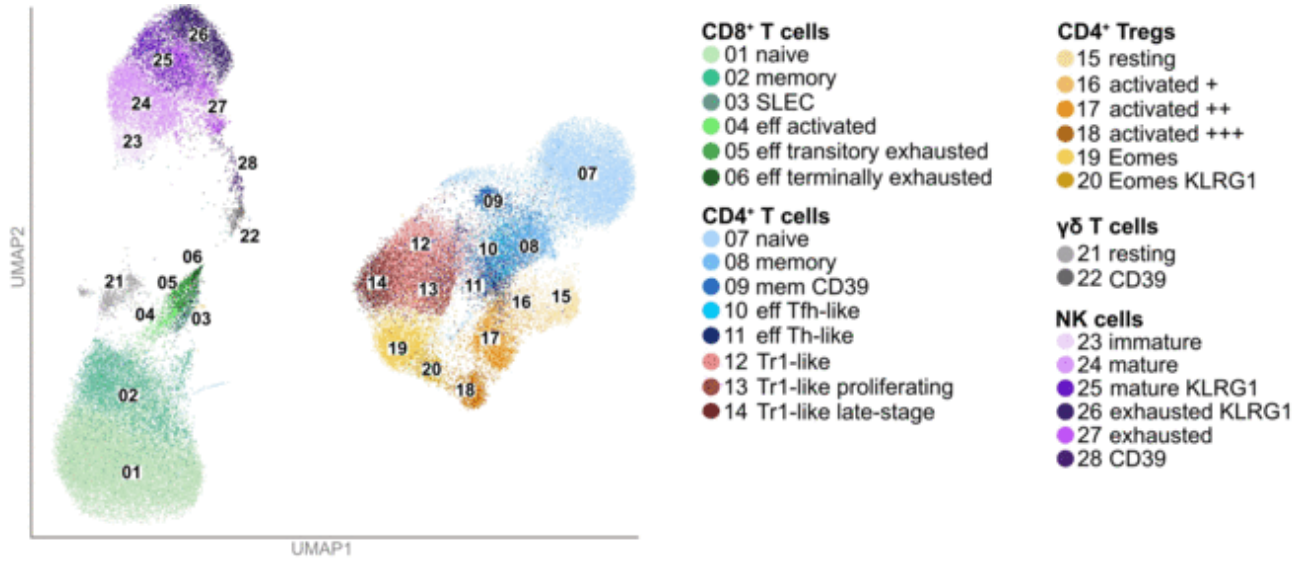
CLL progression was accompanied by coordinated and dynamic remodeling of adaptive and innate immune populations. Within the T-cell compartment, early activation and expansion of effector subsets evolved into progressive dysfunction, characterized by depletion of naïve $CD8^+$ T cells, accumulation of terminally exhausted $CD8^+$ T cells, and increased expression of inhibitory receptors such as PD-1, TIM-3, CD39, and CD101. In parallel, regulatory populations expanded, including Tr1-like $CD4^+$ T cells and activated $FoxP3^+$ regulatory T cells. Notably, we identified a previously unrecognized Eomes- and FoxP3-co-expressing regulatory T-cell (Treg) subset that accumulated during advanced disease. Natural killer cells initially expanded but later underwent differentiation accompanied by the acquisition of exhaustion markers.

High-dimensional profiling of the myeloid compartment showed a marked expansion of immunosuppressive $PD\text{-}L1^+$ patrolling monocytes, the emergence of mature regulatory dendritic cells (mregDCs), and a reduction in conventional type 2 dendritic cells (cDC2s). These changes were accompanied by phenotypic reprogramming consistent with impaired antigen presentation and the promotion of T-cell exhaustion and regulatory T-cell induction.

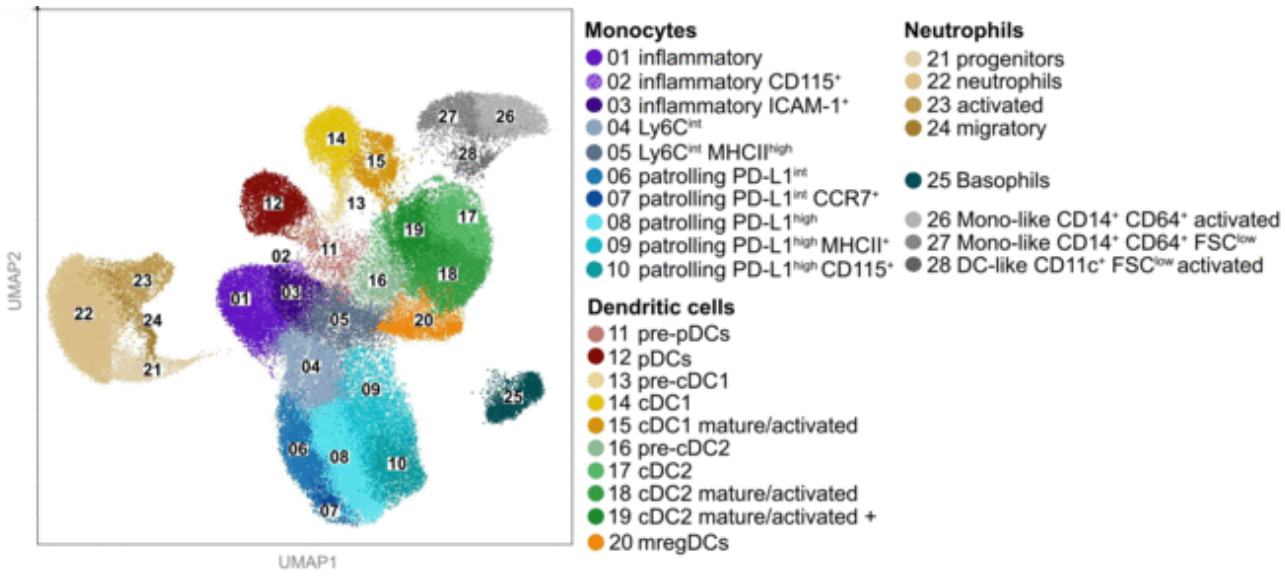
Together, these findings show that CLL progression in the Eμ-TCL1 model follows a stepwise reorganization toward a myeloid-driven, immunosuppressive microenvironment characterized by effector T-cell exhaustion and expansion of regulatory populations. This framework provides deeper mechanistic insight into immune failure in CLL and may guide strategies aimed at reactivating effective anti-leukemic immunity.



Graphical abstract



UMAP of T cells during CLL progression in Eμ-TCL1 mice



UMAP of myeloid cells during CLL progression in Eμ-TCL1 mice